Please consider the remarks herein.

REMARKS

Claims 49-54 and 61-75 are currently pending. An appendix of the pending claims is attached for the Examiner's convenience.

Rejections based under 35 U.S.C § 103

Claims 49-54, 61-63, 65-69 and 71-74 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Walt et al. (U.S. Patent No. 6,327,410 B1, filed September 11, 1998) in view of Brenner (U.S. Patent No. 5,863,722, filed June 7, 1995) and in view of the definitions of Morris ed. (Academic Press Dictionary of Science and Technology, Academic Press, 1992, page 821).

Walt et al. is directed to a microsphere-based analytic chemistry system. Walt et al. teaches the use of microspheres distributed on the surface of a substrate wherein each microsphere contains an optical signature. Regarding claims 49 and 61, from which all claims depend, Walt et al. is silent with respect to teaching at least one subpopulation of microspheres not having an optical signature.

Brenner et al. is directed to a method of sorting polynucleotides through the use of oligonucleotide tags by specifically hybridizing the tags attached to the polynucleotides to their complements on sold phase supports. Contrary to the Examiner's characterization of Brenner et al. that it discloses microspheres not comprising an optical signature, it does not teach or suggest at least one subpopulation of microspheres within an array, not having an optical signature, an aspect of claims 49 and 61, from which all other claims depend.

In contrast, claims 49 and 61 (from which all other claims depend) are directed to a method of determining the presence of a target analyte in a sample through the use of

subpopulations of microspheres randomly distributed on a surface, wherein at least one subpopulation does not contain an optical signature and the use of fiducials to register images of the random array.

As the Examiner is aware, to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 947 F2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Examiner states that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the microspheres not having an optical signature as taught by Brenner et al. and the non-optical encoding taught by Walt et al. to the microsphere compositions of Walt et al. and to provide at least one subpopulation of microsphere without an optical signature thereby eliminating the need to provide optical signatures on all the microspheres for the obvious benefits of simplicity. Applicants respectfully traverse.

As a preliminary matter, neither Brenner et al. nor Walt et al. teach or suggest that at least one subpopulation of microspheres within a random array, does not have an optical signature. Although Brenner et al. discloses the use of microspheres on a substrate, nowhere in this reference is there teaching of the use of microspheres within the same random array, wherein at least one subpopulation does not have an optical signature. Therefore, the requirement that the prior art reference (or references when combined) must teach or suggest all the claim limitations

has not been met. Accordingly the rejection is improper and Applicants respectfully request the withdrawal of the rejection.

In addition, in the instant case there is lacking any suggestion or motivation to modify the references or combine reference teachings. As noted briefly above, the Examiner suggests that one of skill in the art would have been motivated to combine references because it was obvious to apply the microspheres not having an optical signature of Brenner et al. and the non-encoding optical signature of Walt with the microsphere compositions of Walt et al. and to provide at least one subpopulation of microspheres without an optical signature for simplicity. See page 3 of the Office Action.

However, Applicants submit that this is a legally incorrect determination of motivation. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916 F 2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). There is no suggestion in either reference of modifying or combining the references to reach the claims of the present invention. That is, while Walt et al. describes in the use of microspheres for the detecting the presence or absence of a target, there is nothing cited to in either reference that teaches or suggest the use of at least one subpopulation within a random array that does not contain an optical signature.

The Examiner's attention in respectfully drawn to In re Lee, 61 USPQ2d 1430 (CA FC 2002). In this case, the Examiner rejected the claims under 35 U.S.C. §103 and stated that the required motivation "would be that the automatic demonstration mode is user friendly and it functions as a tutorial". Id at 1435. The Federal Circuit stated that "deficiencies of the cited references cannot be remedied by the Board's general conclusions about what is "basic knowledge" or "common sense". The Board's finding must extend to all material facts and must

be documented on the record, lest the "haze of so-called expertise" acquire insulation from accountability. "Common knowledge" and "common sense", even if assumed to derived from the agency's expertise, do not substitute for authority when the law requires authority." (citing In re Zurko, 59 USPQ2d 1693 (CA FC 2001); see Lee, 1434-1435). In the present case Applicants submit that the Examiner has failed to point to anything specific in the cited references that would suggest or provide the motivation to combine the references or to modify them. The Examiner has also failed to document on the record what the common knowledge consists of by pointing to specifics and this is legally incorrect under In re Lee.

In this case, the Examiner has essentially used impermissible hindsight and "common sense" to conclude that the combination of these two references would have been motivated by "the obvious benefit of simplicity ". This is legally incorrect under the Federal Circuit's analysis.

The Examiner makes a very general statement of "obvious benefit". As noted above in the In re Lee case, "common sense" is not an adequate motivation to combine. It is improper to use an obvious to try approach or to cite to only general guidance as to the particular form of the claimed invention or how to achieve it. See In re O'Farrell, 853 F. 2d 894,903, 7 USPQ2d 1673,1681 (Fed. Cir. 1988). Accordingly the rejection is improper and the Applicants respectfully request the withdrawal of the rejection.

Claims 64, 70 and 75 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Walt et al. (U.S. Patent No. 6,327,410, filed September 11, 1998) in view of Brenner (U.S. Patent No. 5,863,722, filed June 7, 1995) and in view of the definitions of Morris ed. (Academic Press Dictionary of Science and Technology, Academic Press, 1992, page 821) as applied to

claims 49 and 61 and further in view of Augenlicht (U.S. Patent No. 4,981,783, filed April 16, 1986)

The distinctions between Brenner et al., Walt et al. and the claims of the present invention are discussed above and are incorporated at this point by reference.

Augenlicht et al. is directed to detecting the expression of cloned genes by immobilizing nucleic acid from individual clones arranged in a pattern on a substrate such as nitrocellulose and hybridizing nucleic acid probes to the immobilized nucleic acid with subsequent determination of the level of expression of individual genes in a sample. Augenlicht et al. teaches the use of fiducial markings to locate the position of the individual clones. Augenlicht et al. does not teach the use of fiducials in an array comprising micropsheres distributed on a substrate. In addition, Augenlicht et al. does not teach the use of microspheres randomly distributed on the surface of a substrate, wherein at least one subpopulation does not have an optical signature.

Claims 64, 70 and 75 are all dependent from claim 49 and as stated above, are drawn a method of determining the presence of a target analyte in a sample through the use of subpopulations of micropsheres randomly distributed on a surface, wherein at least one subpopulation does not contain an optical signature and the use of fiducials to register images of the random array, wherein a first edge of said array is a fiducial edge (claim 64); wherein at least one of said fiducial fibers has a different shape from the others (claim 70); and wherein at least one of said fiducial micropsheres does not comprise a label(claim 75).

As stated above, in order to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation

of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 947 F2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Examiner states that it would have been obvious to one of ordinary skill in the art to modify the substrate of Walt et al. or to modify the fiducial–containing array of Walt et al. by encompassing a fiducial of different shape for the expected benefit of rapid and accurate target analysis as suggested by Augenlicht (claims 64 and 70), (column 8, 15-29), or to modify the different sized fiducials of Walt et al. providing unlabeled fiducials of different size (claim 75) for the obvious benefit of convenience and economy of time and labor. Applicants respectfully traverse.

As a preliminary matter, none of the cited art references teach or suggest the use of at least one subpopulation of microspheres, within a random array, does not contain an optical signature. This is an aspect of the claims of the present invention, therefore the requirement that the prior art reference (or references when combined) must teach or suggest all the claim limitations has not been met.

In determining the differences between the prior art and the claims, the question under 35 U.S.C 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. Stratoflex, Inc. v. Aerowhip Corp., 713 F. 2d 782, 218 USPQ 698 (Fed. Cir. 1983). Here it is claim 49 as a whole that must be considered in determining obviousness, not just the differences between the dependent claim limitations and the prior art. For the reasons set forth above, the rejection is improper and the applicants respectfully request the withdrawal of the rejection.

In addition, in the instant case there is lacking any suggestion or motivation to modify the references or combine reference teachings. The Examiner cites to the obvious benefits of convenience and economy of time and labor and the expected benefit of rapid and accurate target analysis as the motivation to combine references to reach the claims of the present invention.

Obviousness is tested by what the combined teachings of the references would have suggested to those of ordinary skill in the art. It cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. And teachings of references can be combined *only* if there is some suggestion or incentive to do so. *In reFine, 5* USPQ2d *1596, 1599* (CAFC 1988) (quoting *In re Keller,* 208 USPQ 871,881 (CCPA 1981) *and ACS Hosp. Sys. v. Mont efiore Hosp.,* 221 USPQ 929, 933 (CAFC 1984)).

Here, there is lacking any suggestion or motivation in the prior art to arrive at methods of determining the presence of a target analyte through the use of subpopulations microspheres randomly distributed on the surface of a substrate, wherein at least one subpopulation does not contain an optical signature, an element of all claims of the present invention. As noted above, there is no motivation and the Examiner has failed to point to anything specific in the cited references that would suggest the motivation to combine Walt with Brenner and Augenlicht to reach the claims of the present invention. In fact, the combination of these references would not produce the methods of Applicant's invention., because they all lack an essential element as stated above.

As noted above in the In re Lee case, "common sense" is not an adequate motivation to combine. It is improper to use an obvious to try approach or to cite to only general guidance as to the particular form of the claimed invention or how to achieve it. See In re O'Farrell, 853 F. 2d

894,903, 7 USPQ2d 1673,1681 (Fed. Cir. 1988). Accordingly the rejection is improper and the Applicants respectfully request the withdrawal of the rejection.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 781-1989.

Respectfully submitted,
Dorsey & Whitney, LLP

Dated: 1/17/2003

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PENDING CLAIMS

49. A method of determining the presence of a target analyte in a sample comprising:

a) acquiring a first data image of a random array composition comprising:

i) a substrate with a surface comprising discrete sites;

ii) a population of microspheres comprising at least a first and a second subpopulation each comprising a bioactive agent, wherein at least one of said subpopulations does not contain an optical signature; and

iii) a fiducial,

wherein said microspheres are randomly distributed on said surface such that said discrete sites contain microspheres;

b) using said fiducial to register said first data image to create a registered first data image;

c) contacting said random array composition with said sample;

d) acquiring a second data image from said array with said sample;

e) using said fiducial to register said second data image to create a registered second data image; and

f) comparing said first and said second registered data images to determine the presence or absence of said target analyte.

50. The method according to claim 49 wherein said random array comprises a fiber optic bundle and the registration of said first data image utilizes a fiducial fiber.

51. The method according to claim 49 wherein said random array comprises microspheres and the registration of said first data image utilizes a fiducial microsphere.

52. The method according to claim 49 wherein the registration of said first data image utilizes a fiducial template.

53. The method according to claim 49 wherein said bioactive agents are proteins.

54. The method according to claim 49 wherein said bioactive agents are nucleic acids.

61. A method of determining the presence of a target analyte in a sample comprising:

a) providing a registered first data image of a random array composition comprising:

i) a substrate with a surface comprising discrete sites;

ii) a population of microspheres comprising at least a first and a second subpopulation each comprising a bioactive agent, wherein at least one of said supopulations does not contain an optical signature; and

iii) a fiducial,

wherein said microspheres are randomly distributed on said surface such that said discrete sites contain microspheres;

b) contacting said random array composition with said sample;

c) acquiring a second data image from said array with said sample;

d) using said fiducial to register said second data image to create a registered second data image; and

e) comparing said first and said second registered data images to determine the presence or absence of said target analyte.

62. The method according to claim 49, wherein said substrate is selected from the group consisting of glass and plastic.

63. The method according to claim 49 or 62, wherein said registration of said first data images utilizes a fiducial edge.

64. The method according to claim 49 or 62, wherein at least a first edge of said array is a fiducial edge.

65. The method according to claim 51, 52, 53 or 54, wherein said substrate is selected from the group consisting of glass and plastic.

66. The method according to claim 49 or 62, wherein each subpopulation comprises a unique optical signature.

67. The method according to claim 66, wherein said unique optical signature is a bleed-through signature.

68. The method according to claim 49 or 62, wherein each subpopulation comprises an identifier binding ligand that will bind a decoder binding ligand whereby the identification of the bioactive agent is elucidated.

69. The method according to claim 50, wherein said array comprises at least three fiducials, and each of said fiducials is a fiducial fiber.

70. The method according to claim 69, wherein at least one of said fiducial fibers has a different shape from the others.

71. The method according to claim 69, wherein at least one of said fiducial fibers has a different color from the others.

72. The method according to claim 51, wherein said registration utilizes at least three fiducials and each of said fiducials is a fiducial microsphere.

73. The method according to claim 72, wherein at least one of said fiducial microspheres has a different size from the others.

74. The method according to claim 72, wherein at least one of said fiducial microspheres has a different color from the others.

75. The method according to claim 72, wherein at least one of said fiducial microspheres does not comprise a label.